REMARKS

Claims 92-100, 104-108 and 132-137 are now pending in this application.

Claims 1-91 were previously canceled. Claims 101-103 are canceled. Claims 109-131 are canceled.

Claims 92 and 105 are amended to more particularly point out and distinctly claim the invention. The amendment to claim 105 is made in order to correct clerical errors so that the claim is not shown to be dependent upon itself. The amendment to claim 92 is made to clarify that the claimed sequence only encodes Ig domain 2 and Ig domain 3 and the multimerizing component and not other Ig domains of VEGF receptors. New claims 132-137 are supported in the Examples and the original claims. No new matter has been added.

I. Objections to the Specification

The disclosure was objected to because of an embedded hyperlink at page 30. The specification is amended above to remove the hyperlink. The specification has also been amended to indicate that each of the trademarks used are in capital letters followed by a generic description of what the trademark represents. In view of these amendments, the objections to the specification are believed to have been overcome.

II. Rejections under 35 USC 112, first paragraph.

Claims 92-94, 96-98, 100, and 104-108 were rejected for lack of enablement of a nucleic acid molecule encoding VEGF Ig domain 2 downstream of VEGF Ig domain 3.

The rejection is traversed as applied and as it might be applied to the presently pending claims.

Applicants understand the rejection to mean that the Examiner is uncertain with respect to whether the claimed isolated nucleic acid sequence can be broadly claimed to include multiple different orientations in view of the examples provided. In response to the Examiner's concerns applicants have attached a Declaration under 37 C.F.R. §1.132 showing the three different domains combined in a total of six different orientations. This is believed to be sufficient to overcome the Examiner's concerns. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

More specifically, in support of constructs having domains and multimerizing components in different arrangements, Applicants submit a Declaration under 37 CFR 1.132 by Dr. James Fandl describing experiments in which nucleic acid molecules were constructed encoding human Flt-1 domain 2, human Flk1 domain 3 and an Fc multimerizing domain in which the domains are combined in

a total of six different orientations. The experimental results indicate that in each case the constructs encoded a VEGF receptor fusion protein which showed specific binding affinity for VEGF. In light of the experimental results provided in the attached Declaration under 37 CFR 1.132, it is believed this rejection should be withdrawn.

II. Rejections under 35 USC 102(e).

Claims 92-95, 98-97, 100, and 104-108 were rejected as anticipated by US patent No. 6,100,071. The rejection is traversed as applied and as it might be applied to the presently pending claims.

The Examiner has correctly pointed out that the '071 patent suggests chimeric receptor proteins. It may be helpful to distinguish between the two types of receptor molecules disclosed in the '071 patent. The first is a "true" chimeric of domain components from two different VEGF receptors. These molecules are described in Example 3 of the '071 patent as "swap" chimerics and contain the full backbone domains 1, 2, 3, 4, 5, 6 and 7 of either Flt-1 or Flt-4 into which domains from another receptor have been "swapped" in.

The second type of receptor molecule has Ig-like domains from a single receptor fused to an Fc domain. These are truncated receptor molecules which do not include domains from two different receptor molecules. Thus, for example, the '071 patent suggests a truncated receptor which includes only domains 1, 2, and 3 of Flt-1 but has a binding affinity for VEGF equivalent to the wild-type receptor.

Because the '071 patent does not teach a chimeric receptor with less than all seven Ig-like domains, the '071 patent does not anticipate the invention within the meaning of 35 U.S.C. §102. This is because the current claims do not encompass sequences which encode receptor molecules comprised of all seven Ig-like domains.

Applicants recognize that the Examiner could consider rejecting the present claims as *prima facie* obvious over the '071 patent and/or other related art under 35 U.S.C. §103. The Ig-like domains of Flt-1, KDR and Flt-4 have been known for some time even prior to the '071 patent. Further, it has been known for some time that the Ig-like domains of different receptors can be swapped and that some domains are less important than others and might be deleted. However, any *prima facie* case of obviousness can be overcome by demonstrating improved unexpected results, which applicants have obtained with the construct of the invention. Specifically, the claimed isolated nucleotide sequence encodes a three component fusion molecule which combines with an identical molecule to form a dimer. Each component of the fusion protein may be comprised of domain 2 of Flt-1, domain 3 of Flt-4 or Flk-1 (KDR) and an Fc domain of IgG1. Such a fusion protein acts as an effective VEGF trap as disclosed within the attached article Holash et al. (2002) *Proc. Natl. Acad. Sci. USA* 99:11393-11398.

The fusion molecule of the instant invention, as shown within Holash et al., has at least two unexpected properties. The VEGF trap of the invention (termed "R1R2" in Holash et al.) binds VEGF with an affinity (Kd) of about 1 pM whereas the wild-type Flt-1 or KDR receptors bind to VEGF with Kds of about 10 to 20 pM and 75-125 pM, respectively. The Kd of the VEGF trap indicates a stronger affinity. Here, the Kd of 1 is between 10 and 100 times superior to the wild-type receptors.

Still further, experiments comparing a construct made up of domains 1, 2 and 3 of Flt-1 fused to Fc (termed "parent VEGF trap") is prepared within the attached Holash article. This molecule is compared with the fusion protein produced using the nucleotide sequences of the claimed invention. Although both molecules are different in terms of their *in vitro* operability, their properties *in vivo* are even more markedly different. Specifically, the Flt-1 (1, 2, 3)/Fc molecule showed an AUC of 0.04 ug x days/ml compared with 36.28 ug x days/ml for a fusion protein produced using the nucleotide sequences claimed by applicants. Thus, the resulting VEGF trap produced using the claimed nucleotide sequences has markedly improved pharmacokinetic properties relative to a receptor comprised of domains 1, 2 and 3 of Flt-1 which is the type of receptor suggested within the '071 patent. Thus improved, unexpected results demonstrate the unobviousness of the claimed invention.

III. Non-Statutory Double Patenting Rejection.

Claims 92-95, 97-100, 104-105, and 108 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 4, 7 and 8 of co-pending Application No. 10/609,775.

The rejection is traversed as applied and as it might be applied to the presently pending claims. However, applicants wish to expedite prosecution. Accordingly, applicants have attached hereto a signed Terminal Disclaimer with respect to the co-pending application Serial No. 10/609,775 thereby rendering the rejection moot.

Conclusion

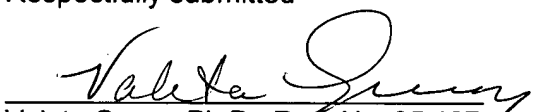
The specification has been amended to correctly refer to the Trademark terms and delete the hyperlink. Although the 35 U.S.C. §112 is not acquiesced to, applicants have submitted a Declaration showing that the different components can be present in different orientations thereby overcoming this rejection. The chimeric molecules actually suggested in the '071 patent include all seven domains. Because applicants' claims are limited to Ig-like domains 2 and 3 of two different receptors combined with a multimerizing component, the invention is not anticipated by the '071 patent. Although no obviousness rejection has been put forth applicants have attached a publication demonstrating that applicants' claimed sequence encodes a molecule which forms a fusion protein which has improved unexpected results relative to a wild-type sequence of any sequence suggested within the '071 patent.

It is believed that this document is fully responsive to the Office action of March 25, 2005. It is believed that the claims are now in condition for allowance, and such action is respectfully urged. However, should the Examiner find that issues remain unresolved Applicants request an interview be arranged prior to the issuance of a Final Rejection.

Fees

Although it is believed that no fees are due, in the event the Patent Office determines that fees are due, the Commissioner is hereby authorized to charge Deposit Account Number 18-0650 in the amount of any fees deemed to be due.

Respectfully submitted



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